

Scientific Abstract

Leber congenital amaurosis (LCA) is a severe early onset retinal degeneration, with diagnosis usually made within the first few months of life. LCA is incurable and untreatable and there is significantly impaired vision present at birth. This progresses to total blindness. This study will focus on the form of LCA caused by mutations in the gene encoding the 65 kDa retinal pigment epithelium (RPE)-specific protein, RPE65. Clinical diagnosis is made by visual function testing. Molecular testing identifies the causative *RPE65* mutations unambiguously.

The investigators believe that collecting safety data in subjects in the intent-to-treat population (that is the population with a higher potential for rescue and vision restoration) appropriately balances risk and potential benefits of an investigational new drug for this devastating disease. A scientifically based study in this population will fulfill the regulatory requirements for administration of investigational pediatric drugs.

Progressive cell loss has been demonstrated to occur in individuals with LCA. A study population composed of children with LCA in the 8-18 year old age group is appropriate for assessing toxicity and safety as patients in this age group show evidence for maintained retinal thickness and cell population. Thus, they possess retinal cells that are viable and amenable to treatment. In contrast, older patients have far fewer cells that could be rescued by treatment.

The vector chosen to deliver the gene is derived from adeno-associated virus (AAV), a nonpathogenic single stranded DNA virus that in the wild requires helper adenovirus for replication. AAV.RPE65 employs AAV as a delivery vehicle for the normal human RPE65 gene.

The study proposed is a phase 1 dosing study to assess the safety of an adeno-associated virus (AAV) based gene transfer material containing a normal human gene encoding the 65 kDa retinal pigment epithelium (RPE)-specific protein, RPE65. The primary objective is to determine the safety and tolerability of retinal administration of AAV.RPE65. Secondary objectives include determination of the dose of AAV.RPE65 that most effectively restores RPE65 activity as determined by visual function and retinal function tests.